CURRENT TOPIC
(CC BY-SA)

UDC: 616.831-005.1-084-082
DOI: https://doi.org/10.2298/VSP230325040P

Possibilities of stroke care improvement in Serbia: consensus document for the prevention, treatment, and rehabilitation of stroke in Serbia

Mogućnosti za unapređenje zbrinjavanja bolesnika sa moždanim udarom u Srbiji: konsenzus dokument za prevenciju, lečenje i rehabilitaciju bolesnika sa moždanim udarom u Srbiji

Viktor Pasovski*, Tanja Novaković†, Mark Parker†, Katarina Katanić Pasovski‡, Ranko Raičević*§

Military Medical Academy, *Clinic for Neurology, ‡Clinic for Ophthalmology, Belgrade, Serbia; †ZEM Solutions, Belgrade, Serbia; §University of Defence, Faculty of Medicine of the Military Medical Academy, Belgrade, Serbia

Key words:
education; serbia; stroke; therapeutics.

Ključne reči:
obrazovanje; srbija; moždani udar; lečenje.

Introduction

A stroke represents an urgent, life-threatening, neurological medical condition that requires immediate attention. Over the past few decades in the field of neurology, especially stroke, we have witnessed the complete recovery of the nervous system after severe clinical manifestations, mainly ischemic but also haemorrhagic strokes. However, stroke is the second cause of death in the Republic of Serbia (RS) and the main cause of disability in adults [1–4].

Globally, over the past three decades, the total number of years lived with disability (Disability-adjusted Life Years, DALYs) due to stroke has significantly increased (from 91.5 million in 1990 to 125 million in 2019, an increase of 33.5 million) [5–7]. There are different trends in countries with high income and those with low to middle income, to which RS belongs. The large increase in the global burden of stroke is not only due to population growth and aging but also due to a significant increase in exposure to important risk factors, such as high body mass index, environmental pollution, high blood glucose levels, high blood pressure, alcohol consumption, physical inactivity, kidney dysfunction, and high temperatures [5–7].

Although there has been a general reduction in standardized incidence, prevalence, mortality, and DALY rates, low to middle-income countries carry the highest percentage of the stroke burden [5, 7]. A large number of strokes could be successfully prevented, representing a significant potential for reducing the burden of stroke, including a significant reduction in long-term consequences. Given the high morbidity and mortality rates, stroke represents a significant medical and socioeconomic problem. The aim of this paper was to define the healthcare system's actions for achieving the best treatment outcomes for stroke patients in RS.

To achieve the best possible health outcomes, it is important to establish priorities and principles for stroke care, including diagnostic and therapeutic protocols spanning from primary prevention to long-term rehabilitation, with a focus on the clinical path as a fundamental component of a doctor's approach. As a result, the Association of Neurologists of Serbia (ANS) approved the development of the "consensus document for the prevention, treatment, and rehabilitation of stroke in RS" [8]. This document offers a comprehensive recommendation for stroke care in RS and serves as a practical guide for clinicians and healthcare professionals, taking into account patients' risks, complications, and evidence-based (EB) approaches to diagnosis and treatment [8]. In 2021, a study was initiated by the ANS and the regional, international consulting agency for health policy and health economics projects, "ZEM Solutions", with the aim of providing a detailed understanding of the current clinical practice for treating stroke patients in RS. To develop the

Correspondence to: Viktor Pasovski, Military Medical Academy, Clinic for Neurology, Crnotravska 17, 11 040 Belgrade, Serbia.
E-mail: viktorpasovski@yahoo.com

Consensus Document (CD) [8], a working group was appointed by the ANS presidency. The working group included major healthcare institutions for stroke care in RS, such as the University Clinical Center of Serbia (UCCS), the University Clinical Center of Vojvodina (UCCV), the University Clinical Center Niš (UCCN), the University Clinical Center Kragujevac (UCCKg), the Military Medical Academy (MMA), the Special Hospital for Treatment of Cerebrovascular Diseases "Sveti Sava", reference Special Rehabilitation Hospitals, and consulting agency "ZEM Solutions".

The CD [8] is based on principles outlined in the National Stroke Guidelines of RS [9], incorporating the best practices observed in the local clinics that adhere to the standards of Good Clinical Practice (GCP). During the development of this document, the latest European and American guidelines for managing stroke patients and stroke prevention were consulted [10–16]. The CD was developed in accordance with the goals of the European Action Plan for Stroke 2018–2030 [17]. Particular emphasis was given to reviewing previous knowledge and clinical experience to ensure the document is tailored to the current state of the healthcare system in RS and enables optimal care for stroke patients.

The working group presented a preliminary draft of the consensus paper to the board of directors of the National Stroke Association of Serbia (NSAS) and the Ministry of Health working group responsible for formulating a national stroke strategy in November 2021. After receiving feedback, the working group addressed the comments and made necessary revisions. The final version was approved in May 2022 during the NSAS Board of Directors meeting, and the complete document has been published and is now available on the ANS website. The recommendations provided, along with the corresponding levels of evidence from the American Stroke Association [15], were used throughout the development of the document.

Recommendations for stroke care improvement in Serbia

The following is included in the CD [8]: prehospital care, emergency assessment and treatment with intravenous and endovascular (EV) therapy, secondary prevention measures starting from initial hospitalization, and primary prevention and rehabilitation measures.

For each of the aspects of stroke care, the recommendations listed in the CD [8] are presented in the following text.

Primary prevention (chapters 3 and 11)

There is significant potential for reducing the burden of strokes in RS by preventing and effectively treating a large number of cases. Roughly 80% of strokes may be averted through the screening and controlling of known risk factors, including actions such as: enhancing hypertension regulation, smoking cessation, preventing diabetes, controlling cholesterol levels, increasing the use of anticoagulants for atrial fibrillation (AF), and eradicating excessive alcohol consumption [18, 19]. As part of primary prevention, various screening models are organized to proactively identify individuals with an increased risk of stroke. To prevent stroke in eligible patients with AF requiring oral anticoagulants (OACs), the European Society of Cardiology (ESC) recommends non-vitamin K antagonist OACs (NOACs) over vitamin K antagonists (VKAs), except in cases involving mechanical heart valves or moderate to severe mitral stenosis [12]. Primary and secondary stroke prevention are addressed by general practitioners, internists, and physicians from various specialties.

Stroke care organization (chapters 10 and 11)

Whether ischemic or hemorrhagic, stroke is a medical emergency that requires urgent attention and offers a high probability of functional recovery. To ensure the timely administration of stroke therapy, it is essential to promptly recognize symptoms, obtain immediate assistance from emergency medical services, and provide effective treatment upon admission to the hospital [20]. The location and availability of emergency medical services are of utmost importance as they play a critical role in ensuring prompt, efficient, and expert triage. That has a significant impact on achieving the established standards for stroke treatment. Air ambulance services greatly reduce the disparities created by the distance of services and transfer between them [21]. A crucial recommendation for enhancing stroke treatment is the organization of hospital services to offer care in specialized stroke units. This type of care is shown to substantially lower mortality rates and reduce the disability burden in stroke patients compared to conventional care in general hospital wards [22]. Improving technical and transportation capabilities can lead to a further reduction in the time it takes to travel from the onset of clinical symptoms to arrival at hospital emergency departments and stroke centers. The development of telemedicine can provide an opportunity for primary healthcare physicians without access to stroke units to seek advice from neurologists and neuroradiologists in acute stroke care and rehabilitation [23]. To ensure that all patients have equitable access, it is essential to increase the number and capacity of comprehensive stroke units (also known as stroke centers or advanced stroke units). In addition, it is necessary to establish a fully operational network of institutions dedicated to stroke care throughout RS and extend the advanced stroke unit network to include major regional general hospitals that possess the necessary resources, such as neurosurgeons, vascular surgeons, 24-hour radiological diagnostics, and intervention specialists.

Hospital treatment of acute stroke (chapters 6 and 11)

Early stroke treatment is essential for reducing the likelihood of complications during the early stages of stroke. Treatment protocols should be based on EB best practices. The administration of *iv* thrombolytic therapy (IVT) using alteplase has been shown to be effective and safe for ischemic stroke (IS) when given within 4.5 hrs of symptom onset and is currently the standard of care. For certain patients who are

eligible for mechanical thrombectomy, tenecteplase may be used instead of alteplase within this therapeutic window. For patients experiencing acute IS and significant intracranial vessel blockage, mechanical thrombectomy (MT) is a recommended treatment option within 6 hrs of symptom onset. In selected cases where multimodal imaging techniques are used, MT may be considered within 16–24 hrs after the onset of symptoms. A multidisciplinary team in stroke units is recommended for the treatment of stroke patients, as it has been demonstrated to improve outcomes and reduce mortality in individuals with acute IS. The hospital system needs to be organized in a manner that brain imaging diagnostic methods are performed within 20 min of arrival at the emergency department for a minimum of 50% of patients who may be eligible for IVT and/or MT.

Secondary prevention (chapters 8 and 11)

The neurology department has a key role in implementing EB medicine, GCP, and national guidelines for secondary stroke prevention. Neurologists should play an active role in secondary stroke prevention alongside general practitioners, internists, and other specialists. Patients with non-cardioembolic IS or transient ischemic attack (TIA) are recommended to use oral antiplatelet drugs to reduce the risk of recurrent stroke and other cardiovascular events, while oral anticoagulant therapy is not advised. An integral component of secondary prevention of IS is the management of hypertension, which involves frequent monitoring of blood pressure and achieving recommended target values of < 130/80 mmHg. As part of secondary stroke prevention, it is recommended to regulate blood glucose levels through lifestyle changes and individual pharmacological therapy. Administering statins is recommended for managing patients with acute IS or TIA who have high cholesterol levels or coronary artery disease. Patients who smoke and have recently experienced TIA or stroke are advised to quit smoking. Patients with recent TIA or non-disabling IS and ipsilateral severe (70–99%) carotid stenosis are advised to undergo carotid endarterectomy (CEA) within two weeks if the perioperative risk of morbidity and mortality is estimated to be less than 6%. Carotid angioplasty and stenting is indicated as an alternative to CEA for symptomatic patients with average or low risk of complications associated with EV intervention when the luminal diameter of the internal carotid artery is reduced > 70% according to noninvasive imaging (ultrasound) or > 50% according to angiography by the North American Symptomatic Carotid Endarterectomy Trial criteria [24]. In secondary prevention of IS, OACs are recommended for all patients with AF. For patients who meet the criteria for NOAC therapy and have no strict contraindications for OAC use, NOACs are preferred over VKAs [12, 16].

Rehabilitation (chapters 7 and 11)

Rehabilitation should be initiated as soon as possible as the main contribution to a positive outcome for stroke survivors and their families. An interdisciplinary approach is considered the best approach for stroke patient rehabilitation.

Long-term care – Life after stroke (chapters 9 and 11)

This is one of the most important aspects of support for stroke survivors and their families.

Our study provides a summarized overview of recommendations and findings for the prevention, treatment, and rehabilitation of stroke in RS with the aim of providing the best possible treatment outcomes for patients in RS. Stroke is a major national health priority, and the importance of our previous publication [8] is significant given the discouraging epidemiological data on stroke in RS [2–4]. It remains the primary cause of death in hospital settings and the second leading cause of overall mortality in the population [2–4]. Improving stroke prevention programs would undoubtedly lead to a reduction in the incidence and morbidity of stroke from the first occurrence. However, two significant barriers to implementing thrombolysis/thrombectomy protocols are high initial costs and a lack of appropriate infrastructure and healthcare resources, resulting in lagging in the goals set by the European Stroke Organization [16]. Addressing these issues will require improvements in the organizational aspects of stroke care, including ensuring equal access to stroke units by increasing their number and capacity and establishing a functional network of stroke care facilities across RS. Based on the data currently available, individuals residing in rural regions of some countries have a lower probability of a favorable stroke outcome compared to those living in urban counterparts [21]. This problem can be solved by improving technical and transport capabilities, introducing Helicopter Emergency Medical Service, and developing telemedicine. The introduction of NOACs to the reimbursement list covered by mandatory health insurance would also contribute to improving stroke prevention in RS [25], as is the case in other reference and neighboring countries such as Croatia [26] and Slovenia [27].

Life after stroke historically has been considered an aspect of rehabilitation. Today, it is acknowledged that immediate attention is necessary and that life after stroke merits recognition in its own right. Due to life after stroke only recently being considered a separate entity, relatively few research studies cover the entire lifespan, those that do focus on reporting outcomes from rehabilitation, and there is little reference to life after stroke in national guidelines [17]. As such, research and recommendations covering life after stroke represent a significant opportunity for stroke care improvement, not just in RS but internationally.

Central and Eastern Europe have led the world in developing a framework for audit and feedback mechanisms, which have proved effective in improving the uptake of EB stroke treatments [28]. Quality monitoring of stroke care using such mechanisms plays an essential role in the timely identification and quantifications of stroke care provision [29] and the communication of evolving issues to those monitoring the registry.

RS currently has four hospitals and nearly 9,000 patients enrolled in the Registry of Stroke Care Quality [30]. In addition

to providing vital information on stroke quality, such registries also form a key evidence source for local cost and burden of stroke studies [31]; it can, therefore, be recommended that this registry be expanded to cover all stroke patients in RS.

Our study was designed to demonstrate the importance of adhering to protocols such as the CD [8] by monitoring specific parameters. That has been convincingly demonstrated through the analysis of the use of novel anticoagulant drugs and the results of mechanical thrombectomy concerning stroke recurrence, outcomes, and treatment costs. In all of these aspects, there was a highly statistically significant association between anticoagulant therapy use in stroke prevention (especially in AF) and the importance of stroke regarding outcomes and direct and indirect treatment costs [32].

In our opinion, this study contributes to understanding current stroke treatment, prevention, and rehabilitation guidelines and serves as a document for primary healthcare and advanced stroke treatment units to take action. It also highlights the importance of EB medicine to healthcare policymakers and regulators.

Conclusion

Although there have been improvements in therapy and prevention, particularly for IS and hemorrhagic stroke, stroke continues to be one of the primary causes of mortality and the primary cause of disability among adults in RS. The clear and comprehensive medical scientific evidence for stroke care shows a great need for substantial investment in stroke care in RS to alleviate the burden of stroke in the country.

Collaborative efforts from various entities, including the Ministry of Health and Social Welfare, other governmental organizations, professional associations advocating for stroke prevention and treatment, such as ANS and NSAS, scientific communities, clinical and preclinical researchers, insurance companies, and industries, are required to implement this approach effectively.

R E F E R E N C E S

1. *Katan M, Luft A.* Global Burden of Stroke. Semin Neurol 2018; 38(2): 208–11.
2. *Institute of Public Health of Serbia "Dr. Milan Jovanović Batut".* Health Statistical Yearbook of the Republic of Serbia 2017 [Internet]. Belgrade, RS: Institute of Public Health of Serbia "Dr. Milan Jovanović Batut"; 2018 [accessed on 2023 August 7]. Available from: https://www.batut.org.rs/download/publikacije/pub2017v026.pdf
3. *Institute of Public Health of Serbia "Dr. Milan Jovanović Batut".* Health Statistical Yearbook of the Republic of Serbia 2018 [Internet]. Belgrade, RS: Institute of Public Health of Serbia "Dr. Milan Jovanović Batut"; 2019 [accessed on 2023 August 7]. Available from: https://www.batut.org.rs/download/publikacije/pub2018.pdf
4. *Institute of Public Health of Serbia "Dr. Milan Jovanović Batut".* Health Statistical Yearbook of the Republic of Serbia 2019 [Internet]. Belgrade, RS: Institute of Public Health of Serbia "Dr. Milan Jovanović Batut"; 2020 [accessed on 2023 August 7]. Available from: https://www.batut.org.rs/download/publikacije/pub2019a.pdf
5. *GBD 2019 Risk Factors Collaborators.* Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet 2020; 396(10258): 1223–49.
6. *GBD 2019 Viewpoint Collaborators.* Five insights from the Global Burden of Disease Study 2019. Lancet 2020; 396(10258): 1135–59.
7. *GBD 2019 Stroke Collaborators.* Global, regional, and national burden of stroke and its risk factors, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Neurol 2021; 20(10): 795–820.
8. *Raičević R, Živanović Ž, Jovanović D.* Consensus document on stroke prevention, treatment and rehabilitation in the Republic of Serbia. Belgrade, RS: Society of Serbian Neurologists, 2022. 43 p. (Serbian)
9. *The Republic's Expert Committee for the Development and Implementation of Good Clinical Practice Guidelines; Ministry of Health of the Republic of Serbia.* National Good Clinical Practice Guidelines for the Diagnosis and Treatment of Ischemic Stroke [Internet]. Belgrade, RS: Agency for Acreditation of Health Care Institutions in Serbia; 2011. (Serbian) [accessed 2023 March 20]. Available from: https://www.zdravlje.gov.rs/view_file.php?file_id=677&cache=sr
10. *Berge E, Whiteley W, Audebert H, De Marchis GM, Fonseca AC, Padiglioni C,* et al. European Stroke Organisation (ESO) guidelines on intravenous thrombolysis for acute ischaemic stroke. Eur Stroke J 2021; 6(1): I–LXII.
11. *Christensen H, Cordonnier C, Kõrv J, Lal A, Ovesen C, Purrucker JC,* et al. European Stroke Organisation Guideline on Reversal of Oral Anticoagulants in Acute Intracerebral Haemorrhage. Eur Stroke J 2019; 4(4): 294–306.
12. *Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C,* et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J 2021; 42(5): 373–498. Erratum in: Eur Heart J 2021; 42(5): 507. Erratum in: Eur Heart J 2021; 42(5): 546–7. Eur Heart J 2021; 42(40): 4194.
13. *Klijn CJ, Paciaroni M, Berge E, Korompoki E, Kõrv J, Lal A,* et al. Antithrombotic treatment for secondary prevention of stroke and other thromboembolic events in patients with stroke or transient ischemic attack and non-valvular atrial fibrillation: A European Stroke Organisation guideline. Eur Stroke J 2019; 4(3): 198–223.
14. *Kobayashi A, Czlonkowska A, Ford GA, Fonseca AC, Luijckx GJ, Korv J,* et al. European Academy of Neurology and European Stroke Organization consensus statement and practical guidance for pre-hospital management of stroke. Eur J Neurol 2018; 25(3): 425–33. Erratum in: Eur J Neurol 2018; 25(10): 1303.
15. *Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K,* et al. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke 2019; 50(12): e344–e418. Erratum in: Stroke 2019; 50(12): e440–1.

16. *Turc G, Bhogal P, Fischer U, Khatri P, Lobotesis K, Mazighi M*, et al. European Stroke Organisation (ESO) - European Society for Minimally Invasive Neurological Therapy (ESMINT) Guidelines on Mechanical Thrombectomy in Acute Ischaemic StrokeEndorsed by Stroke Alliance for Europe (SAFE). Eur Stroke J 2019; 4(1): 6–12.
17. *Norrving B, Barrick J, Davalos A, Dichgans M, Cordonnier C, Guekht A*, et al. Action Plan for Stroke in Europe 2018-2030. Eur Stroke J 2018; 3(4): 309–36.
18. *Gorelick PB*. Stroke prevention. An opportunity for efficient utilization of health care resources during the coming decade. Stroke 1994; 25(1): 220–4.
19. *Gorelick PB*. Stroke prevention. Arch Neurol 1995; 52(4): 347–55.
20. *Kruyt ND, Nederkoorn PJ, Dennis M, Leys D, Ringleb PA, Rudd AG*, et al. Door-to-needle time and the proportion of patients receiving intravenous thrombolysis in acute ischemic stroke: uniform interpretation and reporting. Stroke 2013; 44(11): 3249–53.
21. *Georgakakos PK, Swanson MB, Ahmed A, Mohr NM*. Rural Stroke Patients Have Higher Mortality: An Improvement Opportunity for Rural Emergency Medical Services Systems. J Rural Health 2022; 38(1): 217–27.
22. *Müller R, Pfefferkorn T, Vatankhah B, Mayer TE, Schenkel J, Dichgans M*, et al. Admission facility is associated with outcome of basilar artery occlusion. Stroke 2007; 38(4): 1380–3.
23. *Busti C, Gamboni A, Calabrò G, Zampolini M, Zedde M, Caso V*, et al. Telestroke: Barriers to the Transition. Front Neurol 2021; 12: 689191.
24. *Ferguson GG, Eliasziw M, Barr HW, Clagett GP, Barnes RW, Wallace MC*, et al. The North American Symptomatic Carotid Endarterectomy Trial: surgical results in 1415 patients. Stroke 1999; 30(9): 1751–8.
25. *Republic Fund for Health Insurance (RFZO)*. List of medicines (Lists A, A1, B, C and D) [Internet] 2023 [accessed 2023 May 30]. Available from: https://www.rfzo.rs/index.php/osiguranalica/lekovi-info/lekovi-actual (Serbian)
26. *Croatian Institute for Health Insurance (HZZO)*. Basic list of medicines [Internet] 2023 [accessed 2023 May 30]; Available from: https://hzzo.hr/zdravstvena-zastita/lijekovi/objavljene-liste-lijekova (Croatian)
27. *Institute for Health Insurance of Slovenia (ZZZS)*. Zdravila in živila za posebne zdravstvene namene, razvrščena na listo [Internet] 2023 [accessed 2023 May 30]; Available from: http://www.cbz.si/cbz/bazazdr2.nsf/Search/$searchForm?SearchView (Slovenian)
28. *Mikulik R, Caso V, Bornstein NM, Svobodová V, Pezzella FR, Grecu A*, et al. Enhancing and accelerating stroke treatment in Eastern European region: Methods and achievement of the ESO EAST program. Eur Stroke J 2020; 5(2): 204–12.
29. *Medina-Rioja R, González-Calderón G, Saldívar-Dávila S, Estrada Saúl A, Gayón-Lombardo E, Somerville-Briones N*, et al. Grace Under Pressure: Resiliency of Quality Monitoring of Stroke Care During the Covid-19 Pandemic in Mexico City. Front Neurol 2022; 13: 831735.
30. *Registry of Stroke Care Quality*. RES Q Live Metrics [Internet]. Brno, CZ: Registry of Stroke Care Quality; 2023 [accessed 2023 June 27]. Available from: https://qualityregistry.eu/live-metrics
31. *Benković V, Parker M, Novaković T, Meštrović A, Budinčević H*. The cost of ischaemic stroke in Croatia. Eur Stroke J 2023; 8(1 Suppl): 21–7.
32. *Stroke Alliance for Europe*. The Economic Impact of Stroke [Internet]. Stroke Alliance for Europe; 2023 [accessed 2023 March 15]. Available from: https://www.safestroke.eu/economic-impact-of-stroke/

Received on March 25, 2023
Received on June 30, 2023
Accepted on July 25, 2023
Online First August 2023